UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/418,095	10/14/99	COPLAND III	J UTMB/GAL:239

EXAMINER	
ART UNIT	PAPER NUMBER
1632	5

HM22/0816

MARK B WILSON ESQ
ARNOLD WHITE AND DURKEE
750 BERING DRIVE
HOUSTON TX 77057-2198

NGUYEN,Q

DATE MAILED: 08/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev. 2/95)

US GPO 2000, 465-188/25268

Office Action Summary	Applicati n No. 09/418,095	Applicant(s) COPLAND III ET AL.	
	Examin r Quang Nguyen, Ph.D.	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 8-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the growth of a cancer cell or treating cancer comprising contacting the cancer cell with a thiazolidinedione compound in an amount effective to inhibit the growth of the cancer cell *in vitro* and in nude mice with implanted tumors, does not reasonably provide enablement for the same method *in vivo* in any and all patients, including human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 1-6, 8-15, 25, 28, 29 and 34 are drawn to a method for inhibiting the growth of a cancer cell or treating cancer comprising contacting the cancer cell with a

thiazolidinedione compound in an amount effective to inhibit growth of the cancer cell. Claims 16-24, 26, 27, 33, 35-38 are directed to the same method further comprising contacting the cancer cell with a chemotherapeutic drug or with irradiation (Claims 30-31) or with a therapeutic nucleotide (Claim 32).

The specification teaches a method utilizing troglitazone or other thiazolidinedione compounds such as pioglitazone, rosiglitazone either alone or in combination with other chemotherapeutic agents known in the art to treat cancer. Specifically, the specification discloses that osteosarcoma Saos-2 cells contain functional PPAR-gamma and upon exposing the cells to troglitazone, osteosarcoma cell proliferation measured by total DNA content and thymidine incorporation is inhibited. The specification further teaches that troglitazone is effective in lowering the doses of 5-fluorouracil (5-FU) and doxorubicin required for inhibiting the proliferation of Saos-2 cells. Among the thiazolidinedione compounds tested in this cell culture system, troglitazone is shown to be superior to pioglitazone and rosiglitazone (BRL 49653) in its ability to inhibit cell proliferation. Similar inhibition effects of troglitazone, pioglitazone and rosiglitazone on cell proliferation of human renal URMC 3, 6 and 7 tumor cells were observed. Various human ovarian cancer cell lines including CaOV3, 222, PA-1, 2774, OV CAR3 and SK OV3 were also tested for the proliferation inhibitory effects of the thiazolinedione compounds. The data suggested that responsiveness of individual thiazolidinedione could not be predicted in these ovarian cell lines. Furthermore, in a combined application of taxol and troglitazone to isolated human ovarian tumor cells, an enhanced inhibitory activity over that of either agent used alone was obtained, however

this enhanced inhibitory effect is significantly less than that obtained for the commonly used regimen of taxol and cisplastin already known in the art.

The above evidence is noted and considered. However, it can not be extrapolated to the instant claimed invention which when read in light of the specification encompasses a method of inhibiting the growth of a cancer cell or treating cancer in any and all patients, comprising the utilization of a thiazolidinedione compound. The specification is not enabled for the broadly claimed invention because at the effective filing date of the instant application the therapeutic effect in inhibiting tumor growth of a thiazolidinedione compound *in vivo* is not clearly established in any and all patients, with the exception of nude mice with implanted tumor cells. The recent works from two independent groups demonstrated the unexpected role of troglitazone and rosiglitazone (BRL 49653) in promoting rather than inhibiting the frequency and size of colon tumors in C57BL/6J-APC^{Min}/+ mice (Lefebvre et al., Nat. Med. 4:1053-1057, 1998, Saez et al., Nat. Med. 4:1058-1061, 1998). The *Min* mouse model that is utilized by these groups is a widely used and clinically relevant mouse model for both the human genetic disease familial adenomatous polyposis coli (FAP) and sporadic colon cancer. On the basis of the unexpected findings, Saez et al. stated that "Given the increased colon tumor muliplicity produced by troglitazone in the *Min* mouse, the therapeutic significance of cell culture studies with PPAR-gamma ligands remains to be determined." (column 2, last sentence of second paragraph, page 1060). In addition, Saez et al. noted that breast and prostate cancers share the same risk factor of high-fat diet and expression of PPAR-gamma as colon cancer (column 1, second paragraph,

page 1061), and therefore potentially the use of thiazolidinedione compounds to treat these tumors may have the same deleterious effects as those observed in *Min* mouse. Lefebvre et al. also stated that "These data also caution against the widespread long-term use of insulin sensitizers of the thiazolidinedione class, and indicate that more study is needed before their general use can be recommended." (column 1, last sentence of first paragraph, page 1056). Prior to the reports of Lefebvre et al. and Saez et al., thiazolidinedione compounds (mostly troglitazone, rosiglitazone and pioglitazone) have been demonstrated to have tumor growth inhibitory activity in various cancer cell lines, and in implanted tumors in nude mice in the art (Mueller et al., Mol. Cell 1:465-470, 1998; Brockman et al., Gastroenterology 115:1049-1055, 1998; Kubota et al. Cancer Res. 58:3344-3352, 1998, for examples). Moreover, in light of these studies, Seed noted that "Extrapolating from rodent or *in vitro* studies to clinical trials is known to be perilous and so it would not be tremendously surprising if none of the predicted outcomes, or all of them, were to be observed in subsequent human studies." (Nat. Med. 4:1004-1005, 1998).

The specification of the instant claimed invention fails to provide sufficient guidance, direction and examples demonstrating that the unpredictable therapeutic effects of a thiazolidinedione compound in treating cancerous cells in any and all patients could be overcome, especially with regard to the state of the art at the effective filing date of this application. The specification merely teaches that troglitazone, rosiglitazone and pioglitazone possess anti-tumor growth activity for human osteocarcinoma, renal and ovarian carcinoma cell lines *in vitro* by themselves or in

combination with other well known chemotherapeutic agents (for examples, 5-FU and doxorubicine).

Accordingly, due to the state of the art, and the unpredictability of the therapeutic effects of thiazolidinedione compounds *in vivo* for cancer therapy, the amount of direction and guidance presented together with the absence of *in vivo* working examples, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to use the broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17, 25, 26, 32 and 36-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17 and 25 are improper Markush claims. Each listed species in a Markush claim is supposed to be patentably distinct. However, in claim 17 nitrosourea acts similar as an alkylating agent (as stated in the instant specification on page 36) is listed as a distinct species. In claim 25, intralesional and intramuscular administration of the thiazolidinedione would also be considered as regional delivery. Clarification is requested.

In claim 26, the phrases "suitably dispersed" and "acceptable formulation" are unclear and thus render the claim indefinite. How is a dispersion between a thiazolidinedione and a chemotherapeutic drug considered to be suitable? What is

considered to be a pharmacologically acceptable or non-acceptable formulation? Clarification is requested.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the entry of a therapeutic polynucleotide into a cancer cell, wherein a therapeutic protein encoded by the therapeutic polynucleotide is expressed in an amount effective to inhibit the growth of said cancer cell. Without these steps, the simple step of contacting a cancer cell with a therapeutic polynucleotide may not have any effect on the cancer cell.

Claims 36, 37 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted element is the administered troglitazone and chemotherapeutic drug are effective in inhibition or reduction of cancer cell growth, delay or prevention of metastases. Otherwise, would any simple contacting or perfusion step of any amount of troglitazone and chemotherapeutic drug to a tumor lead to a desirable treatment? Clarification is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

1, 3, 5-7, 9, 10

Claims 1-3, 5-7, 9, 10 and 34 are rejected under 35 U.S.C. 102(a) as being anticipated by Mueller et al. (Mol. Cell 1:465-470, 1998).

The claims are directed to a method for inhibiting the growth of a cancer cell comprising contacting the cancer cell *in vitro* with a thiazolidinedione in an amount effective to inhibit growth of the cancer cell, wherein the thiazolidinedione compound is troglitazone or pioglitaxone, and wherein the cell is a human cell or the cell is from breast and expressing PPAR-gamma. Claim 34 is drawn to a method for inhibiting the cell cycle progression of a mammalian cell comprising contacting the cell with an amount of troglitazone effective to inhibit the cell cycle progression of the cell.

Mueller et al. disclosed that upon exposing cell cultures of human breast cancer 21PT cells expressing PPAR-gamma (See Fig. 1A) with either 10uM of troglitazone or pioglitazone for 4 days or 8 days, treated cells showed a significant decrease in the rate of thymidine incorporation compared to control cultures, indicating a markedly decreased growth rate for the treated breast cancer cells (See Fig. 3B and column 2, second paragraph, page 467). The inhibition of the cell cycle progression in treated breast cancer cells would be an inherent property of the administered troglitazone, and it is evident in no further increase in thymidine incorporation in cells exposed to troglitazone or pioglitazone after 8 days compared with cells treated with troglitazone or pioglitazone for 4 days. Therefore, the reference anticipates the instant claimed invention.

103 Claims 1, 4-7, 9 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Brockman et al. (Gastroenterology 115:1049-1055, 1998).

The claims are directed to a method for inhibiting the growth of a cancer cell comprising contacting the cancer cell *in vitro* with a thiazolidinedione in an amount effective to inhibit growth of the cancer cell, wherein the thiazolidinedione compound is rosiglitazone, and wherein the cell is a human cell or the cell is from colon and expressing PPAR-gamma.

Brockman et al. taught that after 5 days of treating human colon cancer cells derived from cell lines HCA-7, HCT-116, HCT-15 and HCT-15-G25 (expressing exogenous PPAR-gamma) with 1 uM of BRL 49653 (rosiglitazone as defined in the instant specification on page 17, last paragraph), the growth of HCA-7, HCT-116 and HCT-15-G25 cells is inhibited by approximately 25% (See Fig. 3A and column 1, page 1053). The above human colon cancer cell lines have also been demonstrated to express PPAR-gamma (See Fig.1 A & B). Thus, the reference anticipates the instant claimed invention.

DXOP Claims 1, 2, 5-10, 16, 17, 24-29 and 33- 35 are rejected under 35 U.S.C. 102(a) as being anticipated by Elstner et al. (Proc. Natl. Acad. Sci. USA 95:8806-8811, 1998).

Claims 1, 2, 5-10 and 34 are directed to a method for inhibiting the growth of a cancer cell comprising contacting the cancer cell with a thiazolidinedione in an amount effective to inhibit growth of the cancer cell, wherein the thiazolidinedione compound is

troglitazone, and wherein the cell is a human cell or the cell is from breast and expressing PPAR-gamma. Claim 34 is drawn to a method for inhibiting the cell cycle progression of a mammalian cell comprising contacting the cell with an amount of troglitazone effective to inhibit the cell cycle progression of the cell. Claims 16, 17, 24 and 26 are drawn to the same method of claim 1 further comprising contacting the cell with a chemotherapeutic agent (preferably an antineoplastic agent) and wherein the thiazolidinedione and the chemotherapeutic drug are suitably dispersed in a pharmacologically acceptable formulation. Claims 25, 27-29 are directed to the same method of claim 1 wherein the thiazolidone compound is contacted the cell at the same time as contact with the chemotherapeutic agent, and wherein the cancer cell is a tumor cell in a tumor which has been resected. Claims 33 and 35 are directed to a method for treating cancer in a patient comprising administering to the patient troglitazone and a chemotherapeutic drug in an amount effective to inhibit the cancer.

Elstner et al. disclosed that clonal proliferation of human breast cancer cells derived from cell lines MCF7, T47D, MDA-MB-231 (all cells expressed PPAR-gamma, see Fig.2) were inhibited by troglitazone (TGZ) in a concentration-dependent manner (See Fig. 3 and column 2, page 8807). This inhibition was further enhanced with the combination of TGZ and all-*trans*-retinoic acid (ATRA) which is an antineoplastic chemotherapeutic agent (See column 1, page 8806). The reference also taught that culturing human breast adenocarcinoma tissues resected from patients for 4 days in the presence of both TGZ and ATRA resulted in massive apoptosis in each cancer sample, in effect inhibiting cell cycle progression of cancer cells and tumor growth (See column

1, first paragraph, page 8803). Elstner et al. further taught that the administration of TGZ, ATRA or the combination of TGZ and ATRA into immunodeficient mice with implanted MCF-7 tumor cells resulted in a significant inhibition of tumor size and weight (See column 1, second paragraph, page 8809 and Fig. 6). In addition, the reference disclosed that troglitazone was administered into nude mice orally by gavage (regionally to stomach). Therefore, the reference clearly anticipates the claimed invention.

Claims 1, 2, 4-10, 16, 17, 24-29, 33 and 35 are rejected under 35 U.S.C. 102(a) as being anticipated by Kubota et al. (Cancer Res. 58:3344-3352, 1998).

Kubota et al. disclosed that troglitazone and other PPAR-gamma ligands including BRL49653 (rosiglitazone) among others have anti-proliferative effects on the human PC-3 prostate cancer cells (See Fig. 2, Table 1 and page 3346). The reference further disclosed that upon treating surgically removed fresh prostate cancers with troglitazone in tissue cultures for 4 days, most cancer samples exhibited prominent necrotic changes, and in effect cancer cell growth was inhibited (column 2, second paragraph, page 3348). Kubota et al. also taught the combined application of troglitazone and ATRA (an antineoplastic chemotherapeutic agent, see column 2, second paragraph, page 3344) to treat human prostate cancer cells *in vitro* (See Table 1) and to nude mice implanted with PC-3 tumors (See Fig. 7). Although the combined treatment did not result in synergistic effects in nude mice, significant reduction in tumor growth measured in tumor volume and tumor weight was obtained. Troglitazone was administered to nude mice orally through the gavage procedure, which in effect

delivering troglitazone regionally to the stomach. Thus, the reference anticipates the instant claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 9, 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mueller et al. (Mol. Cell 1:465-470, 1998) or Brockman et al. (Gastroenterology 115:1049-1055, 1998) or Kubota et al. (Cancer Res. 58:3344-3352, 1998) in view of Urban and Green (U.S. Patent No. 5,814,647 with a filed date 3/4/1997).

The claims are drawn to a method for inhibiting the growth of a cancer cell comprising contacting the cancer cell with a thiazolidinedione compound in an amount

effective to inhibit growth of the cancer cell, wherein the cancer cell is a bone osteocarcinoma cell, a precursor to osteocarcinoma, an ovarian cell or a renal cancer cell.

The teachings of Mueller et al., Brockman et al. and Kubota et al. have been discussed above. Basically, a thiazolidinedione compound has been demonstrated to inhibit cell proliferation in human breast cancer cells, human colorectal cancer cells and human prostate cancer cells in these references, respectively. However, none of these references taught the use of a thiazolidinedione compound to inhibit cellular growth in osteosarcoma cells, precursor to osteosarcoma, ovarian or renal cancer cells.

Urban and Green taught the use of troglitazone and related compounds in the treatment of the climacteric symptoms. In the specification of the issued patent, Urban and Green stated that troglitazone and related compounds can be used for the treatment of certain types of cancers in addition to the treatment of climacteric (a syndrome of endocrine, somatic and psychological changes occurring at the termination of the reproductive period in the female). A type of cancer that was contemplated to be treated with a thiazolidinedione compound is mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma, rhabdomyosarcomas, fibrosarcomas, hemangiopericytoma and mesotheliomas (See column 3, first two paragraphs).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify a method disclosed by Mueller et al., Brockman et al. or Kubota et al. with the teaching of Urban and Green by substituting

breast, colorectal or prostate cancer cells with osteosarcoma, precursor to osteosarcoma, renal and ovarian cancer cells to arrive at the instant claimed invention. It would have been obvious for one of ordinary skill to test the growth inhibitory effects of a thiazolidinedione compound to any known cancer cell lines or any cancer tissues given its potential therapeutic effects already demonstrated in various breast, prostate and colorectal cancer cell lines. One of ordinary skill would have been motivated to carry out the above modification because troglitazone has been suggested to be useful in adjuvant therapy for breast, prostate and colorectal cancers due to its antiproliferative effects and its low toxicity and well tolerance in humans (See last paragraphs in the Discussion sections of Mueller et al., Brockman et al. or Kubota et al.). Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1 and 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elstner et al. (Proc. Natl. Acad. Sci. USA 95:8806-8811, 1998) in view of Medenica et al. (U.S. Patent No. 5,736,129) and Knight et al. (U.S. Patent No. 6,090,407).

The claims are drawn to a method for inhibiting the growth of a cancer cell comprising contacting the cancer cell with a thiazolidinedione compound in an amount effective to inhibit growth of the cancer cell, and the same method further comprising contacting the cell with a chemothrapeutic drug wherein the chemotherapeutic drug comprises an alkylating agent, a mitotic inhibitor, an antibiotic, a nitrosourea, an antimetabolite, a corticosteroid hormone or an antineoplastic agent.

The teachings of Elstner et al. have been discussed above. Essentially, Elstner et al. taught that the combinatorial administration of troglitazone and a chemotherapeutic agent all-*trans*-retinoic acid (ATRA) synergistically and irreversibly inhibits growth and induces apoptosis of human breast MCF-7 cancer cells *in vitro* and in nude mice with implanted tumor cells (See Fig. 3 and Fig. 6). The reference did not teach a concomitant administration of troglitazone and an alkylating agent, a mitotic inhibitor, an antibiotic, a nitrosourea, an antimetabolite or a corticosteroid hormone in inhibiting the growth of a cancer cell.

Medenica et al. disclosed a method of treating cancer cells by the use a multidrug chemotherapeutic regiment. The utilized drugs that are taught in the issued patent encompass alkylating agents such as Cis-platin, cyclophosphamide; mitotic inhibitors such as etoposide or VP-16, taxol, vinblastine; antibiotics such as doxorubicin, dactinomycin; an antimetabolite such as 5-FU and a corticosteroid hormone such as prednisone (See columns 6-10). Knight et al. taught a method of delivering anti-cancer drugs including a nitrosourea agent such as lomustine, and others such as taxol, 5-FU, etoposide... in treating cancer (See claim 1 on column 16).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify a method disclosed by Elstner et al., with the teachings of Medenica et al. and Knight et al. by substituting ATRA with any or a combination of the disclosed chemotherapeutic drugs. One of ordinary skill in the art would have been motivated to carry out such modification to obtain a more effective combination of drugs in inhibiting cancer cell growth, particularly with regard to the

potential synergistic effects of troglitazone with other commonly used chemotherapeutic drugs besides ATRA. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kubota et al. (Cancer Res. 58:3344-3352, 1998) in view of Frisch (U.S. Patent No. 5,866,550).

The claims are drawn to a method for inhibiting the growth of a cancer cell comprising contacting the cancer cell with a thiazolidinedione compound in an amount effective to inhibit growth of the cancer cell, wherein the thiazolidinedione is contacted with a cancer cell by administering the thiazolidinedione regionally, endoscopically, intravenously, intralesionally, percutaneously, subcutaneously, intraperitoneally, intracheally, intramuscularly, or by perfusion, and wherein the same method further comprising contacting the cell with a therapeutic polynucleotide selected from a group among which is E1A gene.

Kubota et al. taught that treating human prostate PC-3 tumors implanted in immunodeficient mice with oral troglitazone by the gavage procedure (regionally to the stomach) resulted in a significant reduction in tumor growth (See Fig. 7, page 3350). Further reduction in turmor growth was not obtained in a combinatorial treatment of troglitazone and all-*trans*-retinoic acid (ATRA). However, the reference did not teach a combinatorial treatment comprising troglitazone and a therapeutic polynucleotide selected from a group containing E1A gene.

Frishch disclosed a method of converting pathologic hyperproliferative transformed human cells in a tumor in a subject to a non-hyperproliferative state by administering to the subject a nucleic acid sequence encoding E1A having adenovirus E1A activity (See abstract and claims 7-12).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify a method disclosed by Kubota et al., with the teachings of Frishch by further administering into PC-3 tumor bearing nude mice with a nucleic acid sequence encoding E1A taught by Frishch. One of ordinary skill in the art would have been motivated to carry out such modification to determine the potential synergistic effects of said combinatorial treatment in eradicating the implanted PC-3 tumors, and as suggested by Kubota et al. troglitazone may be a useful adjuvant therapy for prostate cancer (column 2, last sentence, page 3351). Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kubota et al. (Cancer Res. 58:3344-3352, 1998) in view of Roth et al. (U.S. Patent No. 5,747,469).

The claims are directed to a method for inhibiting the growth of a cancer cell comprising contacting the cancer cell with a thiazolidinedione compound in an amount effective to inhibit growth of the cancer cell, wherein the cancer cell is a tumor cell in a tumor. Claims 29-31 are drawn to the same method further comprising resecting the

tumor and irradiating said tumor cell with X-ray irradiation, UV-irradiation, gamma-irradiation, or microwaves, and the thiazolidinedione compound is contacted with the cell at the same time as irradiation.

The teachings of Kubota et al. have been discussed above. Kubota et al. did not disclose a method of inhibiting tumor growth utilizing a combination of troglitazone and irradiation. However, Roth et al. disclosed a method of killing cancerous cells using a tumor suppressor gene, p53 in a recombinant retrovirus, in combination with a DNA damaging agent. An embodiment of the invention disclosed by Roth et al. involves the use of gamma-irradiation, X-rays, UV-irradiation or microwaves as a DNA damaging agent in combination with p53 gene transfer to treat cancer (column 8, second paragraph and see claims 51 and 61-67). Roth et al. further noted that a combination treatment is required to prevent local recurrence following primary tumor resection (See column 3, lines 20-25).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify a method disclosed by Kubota et al., with the teachings of Roth et al. by implementing a combination therapy involving the application of troglitazone and irradiation to residual tumor cells following tumor resection in immunodeficient tumor bearing mice to arrive at the instant claimed invention. One of ordinary skill would have been motivated to carry out said modification to determine the efficacy of such combination treatment in preventing the local recurrence of PC-3 tumor following primary tumor resection in nude mice, with a potential clinical application in human. As mentioned previously, Kubota et al. suggested that troglitazone may be a

useful adjuvant therapy for prostate cancer, particularly for patients who have residual disease after surgery or radiotherapy with curative intent (See column 2, last sentence of third paragraph, page 3351). Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kubota et al. (Cancer Res. 58:3344-3352, 1998) in view of Roth et al. (U.S. Patent No. 5,747,469).

The claim is drawn to a method for treating microsopic residual cancer comprising the steps of identifying a patient having a resectable tumor; resecting said tumor; and contacting the tumor bed with troglitazone and a chemotherapeutic drug.

Kubota et al. taught that the combined application of troglitazone and ATRA to human prostate PC-3 tumor bearing nude mice is effective in reducing tumor volume and tumor weight. However, Kubota et al. did not explicitly teach the use of said combined treatment for treating microscopic residual cancer after the primary cancer is resected. Roth et al. taught that a combination therapy is needed to prevent local recurrence following primary tumor resection in order to obtain a long-term survival rate, at least in the case for human NSCLC (column 3, second paragraph). Furthermore, Kubota et al. also suggested that troglitazone can become a useful adjuvant therapy for prostate cancer, particularly for the patients who have minimal residual disease after surgery or radiotherapy with curative intent (column 2, last sentence of third paragraph, page 3351).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify a method disclosed by Kubota et al., with the teachings of Roth et al. by treating nude mice bearing microscopic residual cancer following the resection of the primary tumor with the combination of troglitazone and ATRA to arrive at the instant claimed invention. One of ordinary skill would have been motivated to carry out said modification to determine the efficacy of such combination treatment in preventing the local recurrence of PC-3 tumor following primary tumor resection in nude mice, with a potential clinical application in human as contemplated by both Kubota et al. and Roth et al.. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kubota et al. (Cancer Res. 58:3344-3352, 1998) in view of Medenica et al. (U.S. Patent No. 5,736,129).

The claim is directed to a method for treating a subject having a tumor comprising the step of perfusing said tumor, over an extended period of time, with troglitazone and a chemotherapeutic drug.

The teachings of Kubota et al. have been discussed above. Kubota et al. did not teach the administration of troglitazone and ATRA by perfusion to human prostate PC-3 cancer bearing nude mice. However, Medenica et al. taught in details the use of locoregional intra-arterial infusion or perfusion chemotherapy to treat cancer (Columns 27-30). Medenica et al. further taught that this approach is more effective in delivery the

drug to solid tumors in comparison to the systemic routes of either orally or intravenously, and without dependent on the blood supply to said tumors (column 27, lines 5-26).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify a method disclosed by Kubota et al., with the teachings Medenica et al. by treating tumor bearing mice with troglitazone and ATRA through a locoregional intra-arterial infusion approach rather than through the gavage procedure to arrive at the instant claimed invention. One of ordinary skill would have been motivated to carry out said modification to determine the true therapeutic efficacy of the combination troglitazone and ATRA in treating PC-3 tumor bearing nude mice, with a potential clinical application in human. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, J.D., may be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2801.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Karen M. Hauda

KAREN HAUDA
PRIMARY EXAMINER